

Amendments to the Claims:

This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1. (Currently amended) An antibody recognizing both [[an]] a proteolytic enzyme and a substrate thereof, wherein said antibody is a bispecific antibody which functionally substitutes for a cofactor that enhances proteolysis of the substrate by the enzyme, the enzymatic reaction.
2. (Canceled)
3. (Currently amended) The antibody according to claim [[2]]1, wherein said proteolytic enzyme, substrate, and cofactor are blood coagulation/fibrinolysis-associated factors.
4. (Currently amended) The antibody according to claim 3, wherein the proteolytic enzyme ~~of a blood coagulation/fibrinolysis-associated factor~~ is blood coagulation factor IX and/or activated blood coagulation factor IX; the substrate is blood coagulation factor X; and the cofactor is blood coagulation factor VIII and/or activated blood coagulation factor VIII.
5. (Canceled)
6. (Currently amended) The antibody according to claim [[1]] 4, wherein said antibody comprises [[a]] complementarity determining regions (CDRs) comprising (A) the amino acid sequences of anti-blood coagulation factor IX/IXa antibody H chain CDRs of the following (a1) or (a2) and L chain CDRs of the following (b1) or (b2) or a complementarity determining region functionally equivalent thereto, and a complementarity determining region comprising; and

(B) the amino acid sequences of anti-blood coagulation factor X antibody H chain CDRs of described in any one of the following (b1) to (b9) or a complementarity determining region functionally equivalent thereto: (c1) to (c9) and L chain CDRs of the following (d1) or (d2):

(a1) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 14, 15, and 16, respectively;

(a2) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 18, 19, and 20, respectively;

(b1) L chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 206, 207, and 208, respectively;

(b2) L chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 214, 215, and 216, respectively;

(b1) (c1) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 22, 23, and 24, respectively;

(b2) (c2) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 26, 27, and 28, respectively;

(b3) (c3) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 30, 31, and 32, respectively;

(b4) (c4) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 34, 35, and 36, respectively;

(b5) (c5) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 38, 39, and 40, respectively;

(b6) (c6) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 42, 43, and 44, respectively;

(b7) (c7) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 46, 47, and 48, respectively;

(b8) (c8) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 50, 51, and 52, respectively;

(b9) (c9) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 54, 55, and 56, respectively

(d1) L chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 210, 211, and 212, respectively;

(d2) L chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 218, 219, and 220, respectively.

7. (Previously presented) A composition comprising the antibody according to claim 1 and a pharmaceutically acceptable carrier.

8. (Currently amended) [[The]]A composition comprising the antibody according to claim [[7]] 4, wherein said composition is a pharmaceutical composition used for preventing and/or treating bleeding, a disorder accompanied by bleeding, or a disorder caused by bleeding.

9. (Original) The composition according to claim 8, wherein the bleeding, disorder accompanied by bleeding, or disorder caused by bleeding is a disorder that arises and/or progresses as a result of an activity decrease or deficiency of blood coagulation factor VIII and/or activated blood coagulation factor VIII.

10. (Original) The composition according to claim 9, wherein the disorder that arises and/or progresses as a result of an activity decrease or deficiency of blood coagulation factor VIII and/or activated blood coagulation factor VIII is hemophilia A.

11. (Original) The composition according to claim 9, wherein the disorder that arises and/or progresses as a result of an activity decrease or deficiency of blood coagulation factor VIII and/or activated blood coagulation factor VIII is a disorder in which an inhibitor against blood coagulation factor VIII and/or activated blood coagulation factor VIII is generated.

12. (Original) The composition according to claim 9, wherein the disorder that arises and/or progresses as a result of an activity decrease or deficiency of blood coagulation factor VIII and/or activated blood coagulation factor VIII is acquired hemophilia.

13. (Original) The composition according to claim 9, wherein the disorder that arises and/or progresses as a result of an activity decrease of blood coagulation factor VIII and/or activated blood coagulation factor VIII is von Willebrand's disease.

14. (Withdrawn – currently amended) A method for preventing and/or treating bleeding, a disorder accompanied by bleeding, or a disorder caused by bleeding, wherein said method comprises the step of administering the antibody according to claim [[1]] 4.

15. (Canceled)

16. (Currently amended) A kit used in a method of preventing and/or treating bleeding, a disorder accompanied by bleeding, or a disorder caused by bleeding, wherein said kit comprises at least the antibody according to claim [[1]] 4.

17. (Withdrawn – currently amended) A method of preventing and/or treating bleeding, a disorder accompanied by bleeding, or a disorder caused by bleeding, wherein said method comprises the step of administering the antibody according to claim 4 in combination with blood coagulation factor VIII.

18. (Currently amended) A kit used in a method of preventing and/or treating bleeding, a disorder accompanied by bleeding, or a disorder caused by bleeding, wherein said kit comprises at least the antibody according to claim 4 and blood coagulation factor VIII.

19. (Withdrawn – currently amended) A method for preventing and/or treating bleeding, a disorder accompanied by bleeding, or a disorder caused by bleeding, wherein said method comprises the step of administering the composition according to claim 7.

20. (New) The antibody of claim 4, wherein the antibody

(A) binds the same epitope of blood coagulation factor IX/IXa as an antibody having the H chain CDRs of (a1) or (a2) below and the L chain CDRs of (b1 or (b2) below, and

(B) binds the same epitope of blood coagulation factor X as an antibody having the H chain CDRs of any one of (c1) to (c9) below and the L chain CDRs of (d1) or (d2) below:

(a1) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 14, 15, and 16, respectively;

(a2) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 18, 19, and 20, respectively;

(b1) L chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 206, 207, and 208, respectively;

(b2) L chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 214, 215, and 216, respectively;

(c1) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 22, 23, and 24, respectively;

(c2) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 26, 27, and 28, respectively;

(c3) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 30, 31, and 32, respectively;

(c4) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 34, 35, and 36, respectively;

(c5) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 38, 39, and 40, respectively;

(c6) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 42, 43, and 44, respectively;

(c7) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 46, 47, and 48, respectively;

(c8) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 50, 51, and 52, respectively;

(c9) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 54, 55, and 56, respectively

(d1) L chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 210, 211, and 212, respectively;

(d2) L chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 218, 219, and 220, respectively.

21. (New) The antibody of claim 4, wherein the antibody shows at least 50% competition for binding to either

(A) blood coagulation factor IX and/or activated blood coagulation factor IXa in a competitive inhibition assay with an antibody having the H chain CDRs of (a1) or (a2) below and the L chain CDRs of (b1 or (b2) below, or

(B) blood coagulation factor X in a competitive inhibition assay with an antibody having the H chain CDRs of any one of (c1) to (c9) below and the L chain CDRs of (d1) or (d2) below:

(a1) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 14, 15, and 16, respectively;

(a2) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 18, 19, and 20, respectively;

(b1) L chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 206, 207, and 208, respectively;

(b2) L chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 214, 215, and 216, respectively;

(c1) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 22, 23, and 24, respectively;

(c2) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 26, 27, and 28, respectively;

(c3) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 30, 31, and 32, respectively;

(c4) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 34, 35, and 36, respectively;

(c5) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 38, 39, and 40, respectively;

(c6) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 42, 43, and 44, respectively;

(c7) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 46, 47, and 48, respectively;

(c8) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 50, 51, and 52, respectively;

(c9) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 54, 55, and 56, respectively

(d1) L chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 210, 211, and 212, respectively;

(d2) L chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 218, 219, and 220, respectively.

22. (New) The antibody according to claim 4, comprising:

(a) an anti-blood coagulation factor IX/IXa antibody variable region comprising the amino acid sequence of SEQ ID NO: 13, 17, 85, 205, or 213; and

(b) an anti-blood coagulation factor X antibody variable region comprising the amino acid sequence of SEQ ID NO: 21, 25, 29, 33, 37, 41, 45, 49, 53, 161, 209, or 217.

23. (New) The antibody according to claim 4, comprising anti-blood coagulation factor IX/IXa H and L variable domains comprising a set of six CDR sequences selected from (a1) and (a2) below and anti-blood coagulation factor X H and L variable domains comprising a set of six CDR sequences selected from (b1) and (b2) below:

(a1) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ 1D NOS: 14, 15, and 16, respectively, and L chain CDR 1, 2, and 3 amino acid sequences described in SEQ 1D NOS: 214, 215, and 216, respectively;

(a2) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ 1D NOS: 86, 87, and 88, respectively, and L chain CDR 1, 2, and 3 amino acid sequences described in SEQ 1D NOS: 206, 207, and 208, respectively;

(b1) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ 1D NOS: 22, 23, and 24, respectively, and L chain CDR 1, 2, and 3 amino acid sequences described in SEQ 1D NOS: 218, 219, and 220, respectively;

(b2) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ 1D NOS: 162, 163, and 164, respectively, and L chain CDR 1, 2, and 3 amino acid sequences described in SEQ 1D NOS: 210, 211, and 212, respectively.

24. (New) The antibody according to claim 4, comprising

(A) anti-blood coagulation factor IX/IXa antibody H and L variable domains comprising a set of six CDR sequences selected from (i) and (ii):

(i) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ 1D NOS: 14, 15, and 16, respectively, and L chain CDR 1, 2, and 3 amino acid sequences described in SEQ 1D NOS: 214, 215, and 216, respectively;

(ii) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ 1D NOS: 86, 87, and 88, respectively, and L chain CDR 1, 2, and 3 amino acid sequences described in SEQ 1D NOS: 206, 207, and 208, respectively; and

(B) an anti-blood coagulation factor X antibody variable domain comprising the amino acid sequence of SEQ 1D NO: 21, 25, 29, 33, 37, 41, 45, 49, 53, 161, 209, or 217.

25. (New) The antibody according to claim 4, comprising

- (A) an anti-blood coagulation factor IX/IXa antibody variable domains comprising the amino acid sequence of SEQ ID NO: 13, 17, 85, 205, or 213; and
- (B) anti-blood coagulation factor X antibody H and L variable domains comprising a set of six CDR sequences selected from (i) and (ii):
 - (i) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOS: 22, 23, and 24, respectively, and L chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOS: 218, 219, and 220, respectively;
 - (ii) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOS: 162, 163, and 164, respectively, and L chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOS: 210, 211, and 212, respectively.

26. (New) The antibody according to claim 4, comprising an anti-blood coagulation factor IX/IXa antibody variable domain comprising the amino acid sequence of SEQ ID NO: 13, 17, 85, 205, or 213.

27. (New) The antibody according to claim 4, comprising anti-blood coagulation factor IX/IXa antibody H and L variable domains comprising a set of six CDR sequences selected from (a) and (b):

- (a) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOS: 14, 15, and 16, respectively, and L chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOS: 214, 215, and 216, respectively;
- (b) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOS: 86, 87, and 88, respectively, and L chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOS: 206, 207, and 208, respectively.

28. (New) The antibody according to claim 4, comprising an anti-blood coagulation factor X antibody variable region comprising the amino acid sequence of SEQ ID NO: 21, 25, 29, 33, 37, 41, 45, 49, 53, 161, 209, or 217.

29. (New) The antibody according to claim 4, comprising anti-blood coagulation factor X antibody H and L variable domains comprising a set of six CDR sequences selected from (a) and (b):

(a) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 22, 23, and 24, respectively, and L chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 218, 219, and 220, respectively;

(b) H chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 162, 163, and 164, respectively, and L chain CDR 1, 2, and 3 amino acid sequences described in SEQ ID NOs: 210, 211, and 212, respectively.